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Factors Associated With Hormone Replacement Therapy Use: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To identify factors associated with HRT uptake among women.

Design: A systematic review and meta-analysis to identify factors associated with HRT uptake.

Setting: Retrospective and prospective cohort studies, case–control studies and cross-sectional studies from any country and in any language.

Population: The study population was women aged 40–60 years old.

Methods: We searched Medline, Embase, CINAHL and Cochrane databases to identify studies reporting associations between demographic, behavioural or health-related factors and HRT uptake. Studies were selected if they reported numbers or odds ratios of the factors and HRT uptake. Studies were combined for meta-analysis, reporting odds ratios and 95% confidence intervals. Quality assessment was performed to quantify the risk of bias.

Main Outcome Measures: HRT uptake, defined as 'ever' versus 'never' users.

Results: 5124 papers were identified for title and abstract screening; 136 full texts were screened; 53 were included in meta-analyses. HRT uptake was 53% lower in Black (OR 0.47, 0.30–0.73) compared to White women. Diabetes, obesity and history of stroke or venous thromboembolism were associated with lower HRT uptake (OR 0.71, 0.59–0.85; 0.67, 0.56–0.81; 0.75, 0.63–0.89; 0.78, 0.74–0.0.83 respectively). Osteoporosis and depression were associated with higher HRT uptake (OR 1.64, 1.10–2.45 and 1.69, 1.17–2.43, respectively).

Conclusions: There are differences in HRT uptake by ethnicity and health characteristics. However, findings are not generalisable globally. Our results could aid healthcare professionals and policymakers to address the gaps in HRT uptake and promote healthcare equity.

1 | Introduction

Menopause is a normal part of aging for women, defined as 12 consecutive months without a menstrual period, and typically occurs between the ages of 45 and 55 [1]. The menopause transition, which includes the year of menopause itself and several years prior to menopause known as the perimenopausal period [2], can be associated with a number of symptoms. These may include hot flushes or night sweats (vasomotor symptoms), sleep disturbances and genitourinary symptoms

such as vaginal dryness [3]. Hormone replacement therapy (HRT) is an effective treatment to alleviate perimenopausal and menopausal symptoms [4–6], particularly vasomotor [7] and genitourinary symptoms [8], while sleep benefits may be mediated through treating vasomotor symptoms [9]. HRT is recommended for managing symptoms after taking medical history into consideration [10–13].

There are documented disparities in HRT prescribing in UK primary care; reported prescribing rates in 2018 were 29% lower in GP practices in the most deprived areas compared to those in affluent areas [14]. A US study in 113 menopausal women between 2018 and 2021 reported racial disparities in HRT use, with women of Black ethnicity being 24% less likely to accept HRT compared to White women [15]. However, acceptability of HRT may differ by ethnicity [15].

Some lifestyle factors and health conditions most prevalent in areas of high social deprivation including diabetes [16], obesity [17] and smoking [18, 19] are associated with more severe menopause symptoms. Additionally, the Women's Health Across the Nation (SWAN) study in the US found a higher burden and duration of vasomotor and depressive symptoms and lower quality of life among Black women compared to White women [20]. We aimed to conduct a systematic review and meta-analyses to determine if there are differences in HRT uptake and identify socioeconomic, health and behavioural factors associated with HRT uptake.

2 | Methods

We registered our protocol in the PROSPERO database, registration number CRD42023459154 (www.crd.york.ac.uk). Medline, Embase, CINAHL and Cochrane databases were searched on 10th October 2023 to identify relevant articles published between 1980 and 2023 using detailed search terms related to hormone replacement therapy, menopause and risk factors (Figures S1–S3). Additional articles were identified through backward citation searching and searches in PubMed. Study screening was conducted using Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia [21].

Title and abstract screening followed by a full text review was conducted in duplicate, and conflicts were discussed and resolved by at least two reviewers. We included retrospective and prospective cohort studies, case–control studies and cross-sectional studies among women aged 40–60 years, from any country, in any language, reporting factors associated with HRT use or prescription. Studies in other languages were translated using Google translate. We included articles reporting quantitative sociodemographic, health and behavioural factors in those who received HRT and those who did not. We excluded studies among women with cancer or a history of cancer, life-limiting conditions, endometriosis and polycystic ovary syndrome (PCOS). We also excluded studies among women who had primary ovarian failure, oophorectomy or hysterectomy, because their menopause would have been induced prematurely [22, 23].

Data on the following were extracted manually into a data extraction sheet in Microsoft Excel by six authors (WMM, DA, JH, ET, GG, JAH): first author and year; study title; journal; country; study design; study period; study setting; exposure measures; statistics; sample size; and study population and age. Exposures included (i) demographic: ethnicity, education, income and marital status, (ii) behavioural: physical activity, alcohol consumption and smoking status, (iii) comorbidities: BMI, obesity, cardiovascular diseases, depression, diabetes, cholesterol levels, hypertension and osteoporosis, (iv) gynaecological: oral contraception use, regular mammograms, gynaecological appointments, parity and family history of breast cancer. The outcome was HRT uptake, defined as 'ever' versus 'never' users. We extracted numbers and adjusted and unadjusted odds ratios of HRT uptake for meta-analysis. Studies were excluded from meta-analyses if they reported only *p*-values or correlation coefficients.

Exposures were simplified into binary variables representing presence or absence, or high or low levels, using absence or low as reference groups. We compared Black and White ethnicities for the main analysis, and any ethnicities compared to White ethnicity as secondary analysis because studies reported varying ethnic categories. The number of participants in the white comparator arm was adjusted by dividing by the number of other ethnic groups within a single study to avoid over-counting. Education was categorised into having received further education (college or university) compared to school education. Because of heterogeneity in education levels reporting, we only combined studies reporting raw numbers for university or college with school-level education. Marital status was categorised as married or not married. Social class was categorised as high or low, smoking and alcohol intake as yes or no, and physical activity as presence or absence. Body Mass Index (BMI) and obesity were combined into a binary variable of obesity (BMI ≥ 30 compared to BMI < 30). BMI was also presented as a categorical variable: underweight (BMI ≤ 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9) and obese (BMI 30–34.9). If various cardiovascular diseases were reported separately, these were combined in separate meta-analyses or otherwise grouped as any cardiovascular disease. Comorbidities including diabetes, heart disease, depression and osteoporosis were categorised as presence or absence. Parity was classified as having any children compared to none, and then having either one, two, three or four children. Oral contraceptive use was defined as past or ever use. Mammogram appointments, gynaecology appointments and family history of breast cancer were classified as presence or absence.

Meta-analysis was undertaken for exposures using a Hartung-Knapp-Sidik-Jonkman (HKSJ) random effects model [24] to calculate combined odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between sociodemographic, health and behavioural characteristics and HRT uptake. Where raw numbers were available, these were used to calculate odds ratios; unadjusted or adjusted odds ratios were substituted where raw numbers were unavailable, with preference for adjusted results if both were available. Meta-analysis was performed if three or more studies reported a factor.

Quality assessment was performed to quantify the risk of bias in each paper, using a tool adapted from the QUIPS [25] and Newcastle-Ottawa Scale [26]. The domains for assessing

quality were (i) study population inclusion and exclusion criteria, (ii) definition of exposures and methods of measurement, (iii) definition of outcomes and methods of measurement, (iv) comparison among exposures, (v) addressing confounding and (vi) statistical analysis and reporting. Elements of these domains were rated as 'low', 'moderate', 'high' or 'unclear'. Quality assessment for each paper was undertaken by one reviewer and 10% of the studies were assessed by a second reviewer. We calculated the number of studies reporting each level of bias assessment.

Inconsistency between studies was reported using the I^2 statistic. Statistical analyses were conducted using Stata 18SE [27]. Results were presented as tables, summary and individual factor forest plots. To assess differences in associations of smoking and HRT uptake over time, we conducted subgroup analyses of studies published before 2002 and studies published after 2002, following the Women's Health Initiative publication [28], a trial that assessed long-term effects of HRT among women. Sensitivity analysis was conducted after excluding studies with a high bias rating on either exposure or outcome measurement after the quality assessment.

A patient co-applicant supported us to obtain the study funding and was involved throughout in study management. We recruited an ethnically and socially diverse group of five women who helped us make sense of the results and supported us with finding ways to communicate these back to the communities who needed it most.

3 | Results

Detailed search strategies are in Figures S1–S3. Searches identified 5124 articles from EMBASE ($n = 3027$), Medline ($n = 1696$), CINAHL ($n = 351$), Cochrane ($n = 47$) and other sources ($n = 3$). 1396 duplicates were removed and 3592 of 3728 studies were excluded following title and abstract screening, leaving 136 studies for full-text review. A further 43 studies were excluded, leaving 93 studies for extraction. Of these, data could not be extracted for meta-analysis in 40 studies (Table S1). A duplicate conference abstract was later excluded [29]. The remaining 53 studies (1 208 556 participants) were included in the meta-analyses. The detailed study selection procedure is summarised in the PRISMA flowchart (Figure 1).

Characteristics of the 53 studies included in meta-analyses are shown in Table 1. Studies were published between 1991 and 2024, 13 studies were from the USA, six each from Italy and the UK, five from Australia, three each from Brazil and France, two each from the Netherlands, Denmark and Spain, and one each from 12 other countries. 44 (83%) studies were from high-income countries, and 6 (11.3%) from middle-income countries. 44 studies were of cross-sectional design, two cohort, three case–control, two unspecified and one each: retrospective review of computerised medical records and randomised control trial baseline characteristics. Data for 23 factors were included as follows: demographic (40 studies), behavioural (35 studies), comorbidities (32 studies) and gynaecological (25 studies) (Table 2). Table 3 shows pooled ORs and I^2

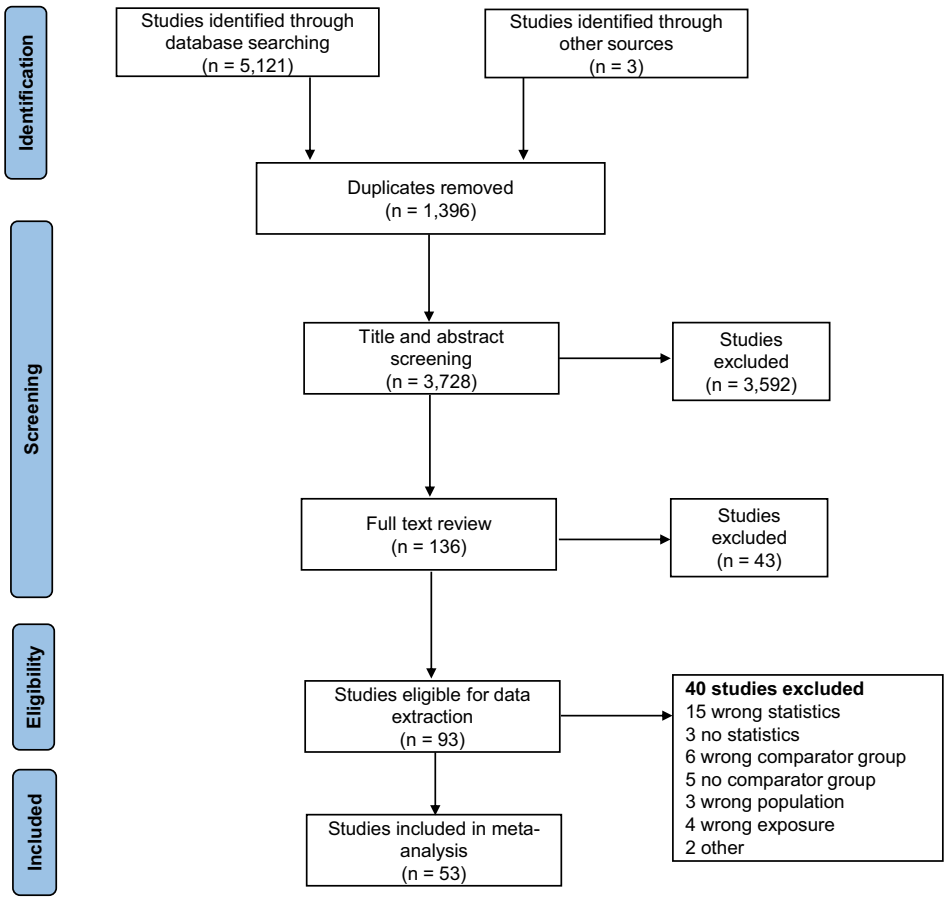

FIGURE 1 | PRISMA flow diagram for study selection.

TABLE 1 | Overview of the characteristics of the studies included for meta-analysis.

Author, year	Year	Country	Study design	Data collection period	Age of population	Sample size	Setting
Amigoni et al. [30]	2000	Italy	Cross-sectional	May–November 1997	44–60	16916	Primary care
Anderson et al. [31]	2016	UK	Retrospective observational study	2015–2016	>45	17936	General population
Aquino et al. [32]	2016	Brazil	Cross-sectional	2008–2010	40–74	3281	General population: civil servants
Bakken et al. [33]	2001	Norway	Cross-sectional	1996–1997	45–64	18199	General population
Bastian et al. [34]	1997	USA	Cross-sectional	1994	45–51	1923	General population
Blanken et al. [35]	2022	USA	Cross-sectional	2014–2015	45–64	200901	Outpatient clinics
Brennan et al. [36]	2004	USA	Cross-sectional	1988–1994	40–80+	3673	General population
Bromley et al. [37]	2004	UK	Prospective matched case–control study	1 January 1992–31 December 1998	45–64	241940	Primary care
Brown et al. [38]	1999	USA	Retrospective review of computerised medical records	1992–1995	50 years or older	8968	General population
Buist et al. [39]	1999	USA	Cross-sectional survey	1995	50–79	703	General population
Carney et al. [40]	2006	USA	Cross-sectional	1996–1999	>40	29851	General population
Cauley et al. [41]	1990	USA	Cross-sectional	October 1986 – October 1988	≥65	9704	General population
Chiaffarino et al. [42]	1999	Italy	Cross-sectional	1992–1996	45–74	1574	Secondary care
Costanian et al. [43]	2018	Canada	Cross-sectional	2010–2013	45–85	10141	General population
DeAloysio et al. [44]	2001	Italy	Cross-sectional	1997–1999	45–75	42464	Menopause clinics
Doamekpor et al. [45]	2023	USA	Cross-sectional	August 2019–May 2020	45–94	2548	General population
Dotlic et al. [46]	2020	Serbia	Cross-sectional	2014–2015	40–65	513	General population
Du et al. [47]	2007	Germany	Unspecified	1997–1999 and 2003–2004	40–79	2248 in 1997–1999 and 2215 in 2003–2004	General population
Duetz et al. [48]	2000	Switzerland	Cohort	1996–1998	55–65	511	General population

(Continues)

TABLE 1 | (Continued)

Author, year	Year	Country	Study design	Data collection period	Age of population	Sample size	Setting
Egeland et al. [49]	1991	USA	Cohort	November 1983–April 1985	42–50	541	General population
Erenus et al. [50]	2007	Turkey	Cross-sectional	2002–2005	44–62	447	Tertiary menopause clinic
Fabre et al. [51]	2010	France	Cross-sectional	1992–2005	45–55+	8433	General population
Gerber et al. [52]	2015	USA	Cross-sectional	2009–2010	>45	157 195	Veterans
Gravena et al. [53]	2013	Brazil	Cross-sectional		45–69	456	General population
Groeneveld et al. [54]	1994	Netherlands	Cross-sectional	1990	45–60	1689	General population
Harris et al. [55]	1999	UK	Cross-sectional	Unspecified	40–59	941	General population
Hess et al. [56]	2008	USA	Unspecified	1996–2002	42–58	3102	General population
Juan-Enrique [57]	2014	Latin American countries	Cross-sectional	Unspecified	45–59	6731	General population
Li et al. [58]	2000	Sweden	Cross-sectional	1996	50–60	3220	General population
Loekkegaard et al. [59]	2002	Denmark	Cross-sectional	1976–1996	45	522	General population
Lokkegaard et al. [60]	2005	Denmark	Cross-sectional	1976–1996	51 and 60	Age 51–440, age 60–273	General population
Low et al. [61]	2006	Australia	Cross-sectional, retrospective, self-reported	2001	60–64	1154	Electoral rolls
Luoto et al. [62]	1998	Finland	Cross-sectional	1992	45–64	1658	General population
MacDougall et al. [63]	1999	USA	Cross-sectional	1993	50–54	288	General population
MacLennan et al. [64]	1993	Australia	Cross-sectional	1991	40–65+	1047	General population
MacLennan et al. [65]	2009	Australia	Cross-sectional	1991–2008		953	General population
Manzoli et al. [66]	2004	Italy	Cross-sectional	1999–2001	50–70	8533	Attending mammography screening
Martinez-Pino et al. [67]	2010	Spain	Cross-sectional	May 2001–June 2005	50–69	21 835	Breast cancer screening

(Continues)

TABLE 1 | (Continued)

Author, year	Year	Country	Study design	Data collection period	Age of population	Sample size	Setting
Mendoza et al. [68]	2016	Spain	Multicentre, observational, Cross-sectional	2016	Under 70	4068	General population
Merom et al. [69]	2002	Israel	Cross-sectional	1998	45–74	704	General population
Mohammed-Cherif et al. [70]	2000	France	Randomised Control Trial baseline characteristics	1994	45–60	592	Trial participants
Moorhead et al. [71]	1997	Britain	Case–control	1981–1990	X	13 379	Unspecified
Nagata et al. [72]	1996	Japan	Cross-sectional	1992	45–64	8608	General population
Pacello et al. [73]	2018	Brazil	Cross-sectional	2012–2013	45–60	749	General population
Pansini et al. [74]	2000	Italy	Cross-sectional		X	17 851	
Parazzini et al. [75]	2008	Italy	Cross-sectional	1997–2003	50–65	1842	General population
Ringa et al. [76]	1999	France	Cross-sectional	1986–1993	45–44	1986 (5266) and 1993 (3942)	General population
Shah et al. [77]	2001	UK	Cross-sectional	1993–1996	40–69	15 256	General population
Taylor et al. [78]	2006	Australia	Cross-sectional	1991–2004	≥15	3015	Data from health surveys
Van Duijnhoven et al. [79]	2006	Netherlands	Cross-sectional	1993–1997	49–70	17 128	General population
Vinker et al. [80]	2003	UK	Cross-sectional	1997	50–70	682	Outpatient clinic
Worsley et al. [81]	2016	Australia	Cross-sectional	October 2013 and March 2014	40–65	2020	General population
Yang et al. [82]	2006	USA	Cross-sectional	2004	40–65	154	General population: women with mobility impairments

TABLE 2 | Number of studies reporting factors potentially associated with HRT uptake.

Factors reported	Number of studies
Sociodemographic and socioeconomic factors	
Ethnicity	
Black vs. White	8
Any ethnicity vs. White (ORs reported in the studies)	9
Education	22
Marital status	22
Comorbidities	
Diabetes	22
Hypertension	18
Osteoporosis	10
High cholesterol	7
Cardiovascular disease	18
Obesity/BMI	21
Hypertriglyceridemia	2
Depression	5
Anxiety	3
Thyroid disease	1
Liver disease	2
Psychotic disorders	1
Behavioural factors	
Smoking	28
Alcohol	11
Physical activity	17
Gynaecological factors	
Parity	13
Ever or past oral contraceptive use	13
Family history of breast cancer	4
Regular mammograms	6
Other factors	

statistics for HRT uptake from meta-analyses. In 39 of the 53 studies, current or ever HRT use ranged from 2.5% to 62% with a median value of 17.6%.

Forty studies reported education level, 22 marital status, 15 ethnicity, 5 income and 4 social class. Results of the associations of sociodemographic factors and HRT uptake are summarised in Table 3. Black women and women from any other ethnic group had lower HRT uptake compared to White women (OR 0.47, 95% CI 0.30–0.73 and OR 0.67, 95% CI 0.59–0.77, respectively) (Table 3, Figure S4a). Education, social class, income and marital status were not significantly associated with HRT uptake (OR 0.81, 95% CI 0.64–1.02; 1.02, 95% CI 0.54–1.91; 0.62, 95% CI 0.25–1.59 and 1.26, 95% CI 0.94–1.69, respectively) (Figures S5 and S6).

Ten studies reported alcohol use, 14 physical activity and 27 smoking status. Results of the associations between behavioural factors and HRT uptake are summarised in Table 3. HRT uptake was 17% higher in current and ever smokers compared to non-smokers (OR 1.17, 95% CI 1.00–1.36). Women engaging in higher levels of physical activity were 22% more likely to take HRT compared with women doing little or no physical activity (OR 1.22, 95% CI 1.04–1.44) (Table 3, Figures S7 and S8). There was no significant association between alcohol consumption and HRT uptake (OR 1.12, 95% CI 0.75–1.68) (Figure S8). In subgroup analyses, HRT uptake was significantly higher in smokers in studies published before 2002 (OR 1.25, 95% CI 1.00–1.55) compared to a non-significant association in studies published after 2002 (OR 1.09, 95% CI 0.87–1.38) (Figure S7).

Eight comorbidities were reported in 32 studies: cardiovascular disease (overall, heart disease, heart failure, myocardial infarction, stroke, venous thromboembolism (VTE)), depression, diabetes, high cholesterol, hypertension, BMI (categorical), obesity (binary) and osteoporosis. Diabetes was reported in 22 studies, obesity and hypertension (17 each), anxiety and heart failure (2 each) (Table 2). BMI categories were reported in 9 studies. Results from the meta-analysis for all comorbidities are shown in Table 3. Obesity, diabetes, history of stroke and VTE were associated with lower HRT uptake. Obese women were 24% less likely to use HRT compared to non-obese women (OR 0.76, 95% CI 0.67–0.88) and for studies that categorised BMI, obese women (BMI 30–34.9) were 35% less likely compared to healthy-weight women (OR 0.65, 95% CI 0.56–0.77) (Table 3, Figure S9). Uptake of HRT was 29% lower in women with diabetes (OR 0.71, 95% CI 0.59–0.85), 25% lower in women with a history of stroke and 22% lower for those with a history of VTE (Stroke 0.75, 95% CI 0.63–0.89; VTE 0.78, 95% CI 0.74–0.83) compared to those without these comorbidities (Figure S10).

Women with osteoporosis were 64% more likely to take HRT (OR 1.64, 95% CI 1.10–2.45) and women with depression were 69% more likely (OR 1.69, 95% CI 1.17–2.43) compared to those without these comorbidities (Figure S11). There was no significant association between HRT uptake and history of cardiovascular disease, heart failure, high cholesterol, hypertension or myocardial infarction (Figures S14 and S15).

Contraception use was reported in 13 studies, parity in 12, family history of breast cancer in 4 and mammogram attendance in 6 studies. Results from meta-analysis of gynaecological factors are shown in Table 3. HRT uptake was significantly higher among women who had used oral contraception (OR 1.51, 95% CI 1.21–1.89), attended regular gynaecology appointments (OR 3.01, 95% CI 1.74–5.20) or had mammogram attendance (OR 1.84, 95% CI 1.03–3.26) (Figure S12). Parity was not significantly associated with HRT uptake for individuals with one, two, three and four children respectively (OR 1.05, 95% CI 0.85–1.30; 1.05, 95% CI 0.76–1.44; 0.92, 95% CI 0.84–1.02 and 0.66, 95% CI 0.37–1.18)

TABLE 3 | Pooled odds ratios for all factors and HRT uptake.

Factors	OR	95% CI	*p*	I^2	Number of included studies
Demographic factors					
Ethnicity					
Black vs. White	0.47	0.30–0.73	0.005	99.6	8
Non-White vs. White	0.67	0.59–0.77	< 0.001	73.2	20
Education					
University/college level vs. school education	0.81	0.64–1.02	0.079	97.5	22
Income					
Highest income vs. lowest income	0.62	0.25–1.59	0.233	95.0	5
Marital status					
Married vs. not married	1.26	0.94–1.69	0.123	93.3	22
Social class					
Highest class vs. lowest class	1.02	0.54–1.91	0.923	84.3	4
Behavioural factors					
Alcohol intake	1.12	0.75–1.68	0.528	99.3	10
Physical activity	1.22	1.04–1.44	0.019	78.6	15
Smoking (overall)	1.17	1.00–1.36	0.046	99.1	27
Smoking sub-group					
Studies published before 2002	1.25	1.00–1.55	0.047	82.3	15
Studies published after 2002	1.09	0.87–1.38	0.409	99.1	12
Comorbidities					
BMI categories – compared to normal BMI					
Underweight BMI	1.04	0.78–1.37	0.720	52.7	4
Overweight BMI	0.87	0.71–1.07	0.153	89.8	9
Obese BMI	0.65	0.56–0.77	0.001	77.4	11
Obesity – binary					
Obese vs. non-obese	0.76	0.67–0.88	0.001	94	17
Diabetes	0.71	0.59–0.85	0.001	88.2	22
Stroke	0.75	0.63–0.89	0.010	49.0	5
Venous Thromboembolism (VTE)	0.78	0.74–0.83	0.004	0.0	3
Cardiovascular disease (overall)	0.79	0.47–1.35	0.328	94.3	7
Cardiovascular disease (sub-group)					
Studies published before 2002	0.75	0.23–2.46	0.403	91.1	3
Studies published after 2002	0.82	0.25–2.67	0.624	92.3	4
Heart disease	0.92	0.74–1.13	0.345	86.5	8
Myocardial Infarction	0.80	0.54–1.18	0.166	46.1	4
Depression	1.69	1.17–2.43	0.020	94.3	4
High Cholesterol	0.96	0.71–1.3	0.761	95	9

(Continues)

TABLE 3 | (Continued)

Factors	OR	95% CI	*p*	I^2	Number of included studies
Hypertension	0.98	0.83–1.16	0.819	96.6	17
Osteoporosis	1.64	1.10–2.45	0.020	98.8	10
Gynaecological factors					
Breast cancer family history	0.76	0.38–1.54	0.310	87.3	4
Contraception use	1.51	1.21–1.89	0.002	94.6	13
Gynaecology appointments	3.01	1.74–5.2	0.002	84.5	8
Regular mammograms	1.84	1.03–3.26	0.042	98.1	6
Parity (any children vs. none)	0.96	0.84–1.10	0.539	88.6	20
Parity (by number of children)					
1 child	1.05	0.85–1.3	0.607	87.0	8
2 children	1.05	0.76–1.44	0.756	94.5	9
3 children	0.92	0.84–1.02	0.101	0.0	7
4 children	0.66	0.37–1.18	0.107	81.3	4

compared with none (Figure S13). There was no significant association between having a family history of breast cancer and HRT uptake (OR 0.76, 95% CI 0.38–1.54) (Figure S13).

Quality assessment results are shown in Figure 2 and Table S2. For study population, 45 studies had a low risk of bias score on recruitment period, compared to 18 with a high bias score for exclusion criteria. For exposure measurement, 45 studies scored low under method and setting, while only two had a high risk of bias for exposure definition. For comparability and outcome measurement, 45 studies had low bias under method and setting, with four showing high bias for outcome and control definitions. For confounding, 30 studies had low bias for valid confounder measurement, while 15 had high bias under confounding methods. On analysis and reporting, 48 studies scored low for result reporting, and three scored high. Five studies had a high bias rating on exposure or outcome measurements and were excluded from sensitivity analysis of association of all factors and HRT uptake: exposure measurement [30, 55], outcome measurement [50, 51, 55, 60]. In a sensitivity analysis, pooled odds ratios for the association of all factors and HRT uptake after excluding studies with a high risk of bias rating for exposure or outcome measurement only in comparison to initial results are summarised in Table S3. There were either no or marginal differences between the main analysis and sensitivity analyses.

4 | Discussion

4.1 | Main Findings

Our systematic review and meta-analysis determined factors associated with HRT uptake. HRT uptake was on average 53% lower in Black ethnic groups compared to White, with 95% confidence intervals suggesting as little as 27% or as much as 70% lower. Among other ethnic groups, uptake was 33% lower (ranging from 23% to 41% lower) in studies conducted in North America and the UK. Uptake was also, on average, lower among those with obesity, diabetes, stroke and VTE compared to those without these conditions. Higher levels of physical activity, being a smoker, living with depression, osteoporosis and attending gynaecological services and mammogram appointments were associated with higher HRT uptake.

4.2 | Strengths and Limitations

We have undertaken the first systematic review and meta-analysis of factors associated with HRT uptake to our knowledge, and we included studies from any country and language. We used random effects meta-analysis using the Hartung-Knapp-Sidik-Jonkman (HKSJ) model, which would minimise having spuriously significant findings [24]. We used subgroup and sensitivity analyses where possible to examine further differences. Duplicate screening and data extraction checking were used to minimise the risk of errors. Combining the Newcastle-Ottawa scale and the QUIPS scale increased the relevance of quality assessment.

There are, however, some limitations. Most studies in our meta-analysis were published more than 20 years ago, and prescribing practices have changed over time. Consequently, we conducted subgroup analyses to compare associations with HRT uptake in older and more recent publications. Studies were primarily from the US and Europe, so our results cannot be generalised, particularly for low- and middle-income countries. Additionally, we were unable to compare uptake between different ethnic groups as most studies only reported HRT uptake in Black and White ethnicities consistently. We did not have information on the type of HRT formulations used in most studies, making it challenging to determine context; for example, transdermal formulations are potentially safer for those with cardiovascular risks and recommended by NICE for women with a BMI > 30 kg/m^2 [83]. Additionally, we were unable to determine if study participants were co-prescribed psychiatric medications, which affects our interpretation of HRT

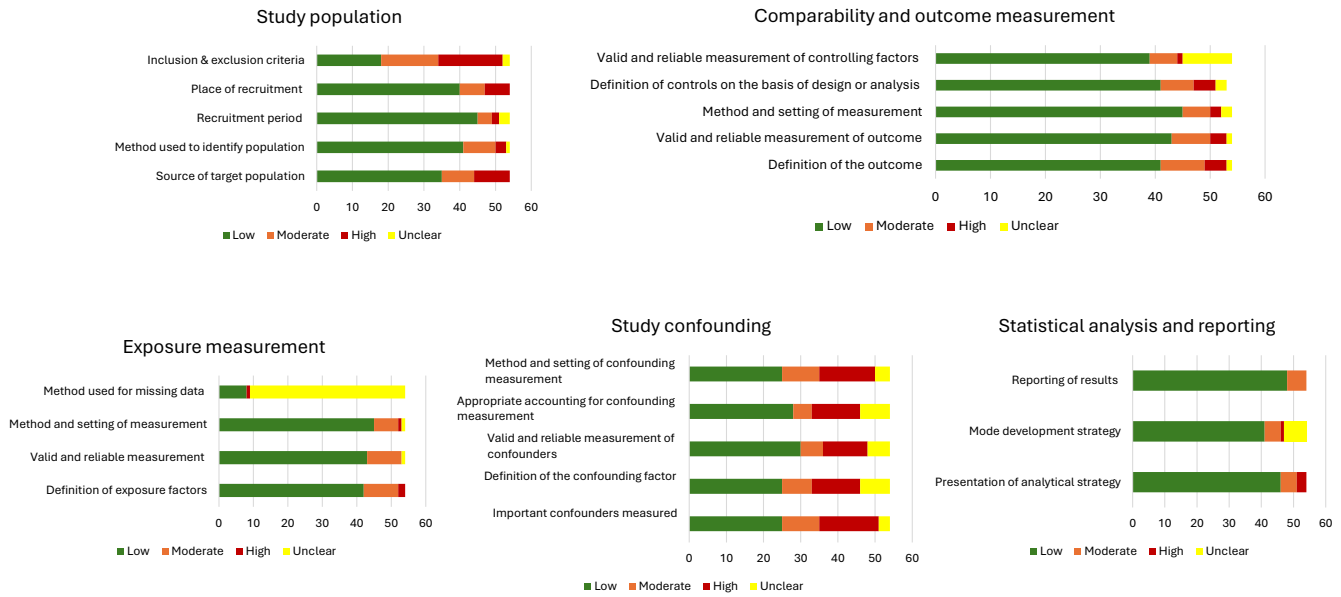

FIGURE 2 | Quality assessment of studies included in meta-analysis.

use and depression. Education, income and social status were reported differently across studies, hence impossible to include in meta-analysis. Considerable heterogeneity among studies introduced uncertainty around the pooled estimates. For instance, HRT uptake among Black women may be 27%–70% lower than in White women. Although these are average effects, the HKSJ model we used supported the significance of effect.

4.3 | Interpretation

This study found significantly higher HRT uptake in those of White ethnicity compared to all other ethnicities. Previous research has documented ethnic inequalities in healthcare [84, 85]. For instance, Black populations may have lower socioeconomic status and levels of education in England, and cultural or language barriers [86, 87], which may impact health-seeking behaviour or access to care. Additionally, women from some ethnic groups feel unrepresented in mainstream menopause communications [87] and there may be a lack of awareness about menopause in some ethnic groups which may impact ability to communicate symptoms [87]. There is evidence that Black and Hispanic women are more likely and Asian women are less likely, to report menopause symptoms [88], and Black (hot flushes), Indigenous (painful sex) and Middle Eastern (weight changes) and mixed races (skin or hair changes) may experience more severe menopausal symptoms compared to White women [89]. Obesity is closely related to socioeconomic disadvantages both in the UK and across the globe [90] and higher BMI is also associated with a higher risk of cardiovascular disease [91], which may impact willingness to prescribe HRT in obese individuals [92–94]. There are, however, reports that menopausal symptoms are more severe in women with higher BMI [95, 96]. Nevertheless, when BMI is over 30, NICE guidelines suggest transdermal over oral HRT [83].

Our meta-analysis has found that diabetes, a risk factor for cardiovascular disease, was associated with significantly lower HRT uptake. This is consistent with our parallel work analysing English primary care records, which found that HRT prescribing in those with type 2 diabetes was 29% lower compared to those without [97, 98]. Having a history of stroke and VTE was associated with significantly lower HRT uptake, likely because oral HRT significantly increases the risk of stroke and VTE [99, 100]. As such, our observed 25% and 22% reduction in HRT uptake among women with stroke and VTE respectively is smaller than expected, suggesting variation in prescribing behaviour or lower comorbidity severity. Similarly, the absence of significant associations between history of heart disease, heart failure, high cholesterol, hypertension or myocardial infarction and HRT uptake should be interpreted judiciously since HRT use in women with cardiovascular conditions is prescribed cautiously with specialist advice [83, 101–102].

Smoking was associated with significantly higher HRT uptake. This is surprising as smoking is often more prevalent in more deprived socioeconomic groups [103] and lower socio-economic status is associated with lower HRT uptake [14]. Additionally, the risk of VTE increases with smoking [104], which may be an indicator for cautious prescribing [105, 106]. The association between smoking and higher HRT uptake observed in older studies was no longer evident after 2002, reflecting cautious HRT prescribing following the WHI study publication [28] and declining global smoking rates [107]. Higher levels of physical activity were associated with higher HRT uptake, but higher levels of physical activity are also associated with less severe menopausal symptoms [108, 109]. Physical activity, often in addition to HRT treatment, is recommended for managing bothersome menopause symptoms by general practitioners, menopause charities and national health campaigns [110]. Physical activity is higher in groups with higher socioeconomic status [111], which is consistent with previously observed patterns in HRT prescribing [112].

We found an association between using gynaecological services and higher HRT uptake. In some countries, patients consult a gynaecologist for HRT; therefore, those who already attend gynaecology appointments may be more likely to take HRT. Some countries in our review have private models of healthcare which may contribute to the affordability of HRT.

Depression was associated with higher HRT uptake. There is evidence that HRT improves depressive symptoms during menopause [113, 114], and our study suggests that higher proportions of women with depression use HRT compared to those without. However, NICE guidelines recommend HRT use for menopause-related depressive symptoms unlike clinical depression [83]. It is unclear whether our observed association was due to appropriate HRT use or even possible overuse. Finally, it was unsurprising that osteoporosis was associated with higher HRT uptake, as HRT is effective in the prevention of fragility fractures and treatment of osteoporosis in post-menopausal women [115–118]. While our review explored socioeconomic, behavioural and health factors associated with HRT uptake, the reasons may be multifactorial, including societal and cultural factors or differences in medical advice or prescribing practices; hence, they should be interpreted with caution.

5 | Conclusion

This work has identified important differences in HRT uptake by sociodemographic, behavioural and health factors. Some differences may be driven by personal choice, access, affordability or lack of information and understanding by the patient. Additionally, clinician knowledge and beliefs regarding HRT risks and benefits may have influenced prescribing patterns. This work suggests that some women who may benefit from HRT are not receiving it, and that HRT uptake among other groups may be less restricted, highlighting the need for continued evaluation of HRT prescribing and use to ensure alignment with current clinical recommendations. Our results could also aid healthcare workers and policymakers to address the gaps in HRT use and prescription and promote healthcare equity. It is unclear whether clinicians have sufficient information to support women in decision-making and how HRT risks and benefits are discussed, as this was out of the scope of our objectives. Future work is needed to explore barriers to HRT uptake and to assess individualised risks and benefits of HRT to inform women's choices. Women's health research is also needed in LMICs.

Author Contributions

Six authors (W.M.M., D.A., E.T., G.G., J.H. and J.A.H.) participated in the study screening and selection, data extraction and meta-analysis. W.M.M. drafted and revised all versions of the manuscript, integrating input from co-authors. L.T. contributed to funding acquisition and study management. All authors reviewed and approved the final version of the manuscript.

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Ethics Statement

The review used published data only and ethical approval was not required.

Consent

The authors have nothing to report.

Conflicts of Interest

Dr. Sarah Hillman was sponsored by the pharmaceutical company Besins to attend the 2024 International Menopause Society Conference. No other authors declare competing interests.

Data Availability Statement

The authors have nothing report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Search strategy in Medline and EMBASE. **Figure S2:** Search strategy in CINAHL. **Figure S3:** Search strategy in Cochrane database of RCTs. **Figure S4:** Ethnicity and HRT uptake. **Figure S5:** Association of education and HRT uptake. **Figure S6:** Social class, income, marital status and HRT uptake. **Figure S7:** Smoking and HRT uptake. **Figure S8:** Alcohol consumption, physical activity and HRT uptake. **Figure S9:** BMI, obesity and HRT uptake. **Figure S10:** Diabetes, stroke, Venous thromboembolism (VTE) and HRT uptake. **Figure S11:** Osteoporosis and depression and HRT uptake. **Figure S12:** Contraception use, regular gynaecology appointments, regular mammograms and HRT uptake. **Figure S13:** Anxiety, family history of breast cancer, parity and HRT uptake. **Figure S14:** Heart disease, heart failure, myocardial infarction, cholesterol and HRT uptake. **Figure S15:** Hypertension, cardiovascular disease and HRT uptake. **Table S1:** Studies excluded for meta-analysis. **Table S2:** Quality assessment of studies included for meta-analysis. **Table S3:** Pooled odds ratios for all factors and HRT uptake after excluding studies with a high bias score on exposure or outcome measurement of quality assessment in comparison to initial pooled statistics.